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Deltoid muscle morphometry as an index of impaired skeletal muscularity in neonatal intensive care

Theodore Dassios[1,2,3], Ourania Kaltsogianni[1], Miltiadis Krokidis[4], Ann Hickey[1], Anne Greenough[2,3,5]

Email address of authors:

Theodore.dassios@nhs.net

Raniagk1@hotmail.com

Miltiadis.krokidis@addenbrookes.nhs

annhickey@nhs.net

anne.greenough@kcl.ac.uk

Address for Correspondence: Professor Anne Greenough, NICU, 4th Floor Golden Jubilee Wing, King's College Hospital, Denmark Hill, London, SE5 9RS, Tel: 0203 299 3037; fax: 0203 299 8284; email: anne.greenough@kcl.ac.uk

[1] Neonatal Intensive Care Centre, King's College Hospital NHS Foundation Trust, London, UK;

[2] MRC-Asthma UK Centre in Allergic Mechanisms of Asthma, King's College London, UK;

[3] Women and Children's Health, School of Life Course Sciences, Faculty of Life Sciences and Medicine, King's College London, UK;

[4]Department of Radiology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK;

[5]National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London; UK

ABSTRACT

We hypothesised that extremely premature infants would have decreased muscle mass at term-corrected age compared to term-born infants and that the degree of reduced muscle mass acquisition would correlate with the duration of invasive mechanical ventilation. The MRI brain scans of infants admitted in the neonatal unit at King's College Hospital between 1/1/2010 and 1/6/2016 were retrospectively reviewed. The coronal cross-sectional area of the left deltoid muscle (DCSA) was measured in 17 infants born <28 weeks of gestation and in 20 infants born at term. The prematurely born infants had a median(IQR) gestation age of 25(24-27) weeks and the term infants 40(38-41) weeks. The duration of invasive mechanical ventilation for the prematurely born infants was 39(14-62) days and for the term infants for 4(2-5) days, p<0.001. DCSA was smaller in prematurely-born infants (median 189, IQR:176-223mm^2) compared to term-born infants (median 302, IQR 236-389mm^2), p<0.001. DCSA was related to gestation age (r=0.545, p=0.001), weight z-score at MRI (r=0.658, p<0.001) and days of invasive mechanical ventilation (r=-0.583, p<0.001). In conclusion, extremely premature infants studied at term had a lower muscle mass compared to term-born infants.

Conclusion: Our results suggest prolonged mechanical ventilation in infants admitted in neonatal intensive care is associated with reduced skeletal muscle mass acquisition.

KEY WORDS: Deltoid muscle morphometry, impaired skeletal muscularity, neonatal intensive care

ABBREVIATIONS

DCSA	Deltoid cross-sectional area
IQR	Interquartile range
MRI	Magnetic Resonance Imaging

AUTHORS SUMMARY

What is known:

- Prolonged mechanical ventilation in adult intensive care patients has been associated with skeletal muscle dysfunction and atrophy.
- The cross-sectional area of the deltoid muscle has been used to evaluate muscle atrophy in infants with a previous branchial plexus birth injury.

What is new:

- Premature infants studied at term exhibit lower cross-sectional area of the deltoid muscle than their term counterparts.
- Prolonged mechanical ventilation could be associated with skeletal muscle impairment.

INTRODUCTION

Following birth, prematurely-born infants commonly spend a long period in neonatal intensive care where they often undergo invasive mechanical ventilation. The effect of critical illness on the skeletal muscles, commonly referred to as “critical illness myopathy”, has been well-described in adults. The most common predisposing conditions in adult intensive care patients are acute respiratory disorders such as acute respiratory distress syndrome, pneumonia and severe asthma [6, 13]. In addition, use of high-dose steroids, non-depolarizing blocking agents [2], aminoglycosides [19] and acidosis [14] may also predispose to critical illness myopathy.

In prematurely born neonates, the postnatal nutritional target is the accretion of body weight at a rate similar to that achieved during intrauterine development [1]; that gold standard, however, is infrequently achieved [4, 5] especially in the sickest infants who rely for long periods on parenteral nutrition. The “weight-targeted” nutritional approach fails to detect qualitative differences in body composition and weight accretion, predominantly in the form of adipose tissue, does not necessarily translate to better outcomes [9]. This is particularly relevant in the prematurely born population whose adult-life adiposity profile might place them at an increased risk for cardiovascular and metabolic disease [15].

Few studies have reported data on qualitative body composition in prematurely born compared to term-born infants [16] and to our knowledge none has specifically investigated skeletal muscle mass. The magnetic resonance imaging (MRI) appearance of the deltoid muscle has been used to evaluate muscle atrophy in infants with a previous branchial plexus birth injury [10, 17]. The cross-sectional area of the deltoid muscle (DCSA) on the affected

side has been shown to be significantly decreased compared to the unaffected size with a mean affected to normal ratio of 76% [17]. The deltoid muscle is often included in the coronal images of MRI-brain scans that prematurely born infants have to assess ventricular dilatation and periventricular leukomalacia and term infants for evidence of white matter injury secondary to hypoxic ischemic encephalopathy (HIE).

We hypothesised that DCSA would be smaller in prematurely born infants studied at term compared to term born infants and that the DCSA would correlate with body weight and gestational age. We also hypothesised that DCSA would correlate with days of ventilation and days of parenteral nutrition. Our aims were to test those hypotheses.

METHODOLOGY

Subjects

The MRI brain scans of infants that were admitted to the neonatal unit at King's College Hospital NHS Foundation Trust, London, UK and underwent a scan between 1 January 2010 and 1 June 2016 were retrospectively reviewed. Two groups of infants were assessed: term-born infants with HIE and extremely prematurely born infants (<28 weeks of gestation at birth) scanned at term that had periventricular leucomalacia or ventricular dilatation diagnosed and sequentially assessed by cranial ultrasonography. The Research and Development department confirmed that the data collection was consistent with a service evaluation/audit, and as such did not require research ethics approval. The study was registered with the Clinical Governance Department of King's College Hospital NHS Foundation Trust.

Calculation of DCSA

Infants were scanned on a 1.5 T MR imager (Siemens, Erlanger, Germany). After localizer sequences, T1-weighted in axial, oblique coronal (angled to the temporal lobe) and oblique sagittal planes were obtained (TR/TE 4000/126 msec: base resolution: 256 mm). T2-weighted images in axial, oblique coronal (angled to the temporal lobe) were obtained (TR/TE 4000/126 msec: base resolution: 256 mm. The slice thickness was 4 mm for all sequences. The field of view was 200x200 mm for T1-weighted images and 220x220 mm for T2-weighted images).

The deltoid muscle was visualised on the oblique coronal plane at the level where the head of the humerus had the maximum diameter at which level the area of the deltoid is maximal [17]. Free-hand tracing of the perimeter of the left deltoid muscle was undertaken by a consultant radiologist (MK) and the DCSA was calculated in mm^2 by the Sectra PACS software (Sectra AB, Linköping, Sweden) (Figure 1). The radiologist performing the DCSA measurement was unaware of the infant's clinical condition and demographics.

Information from the medical records

Gender, gestation age at birth, birth weight and postmenstrual age, postnatal age and weight at the time of MRI were recorded. Data also recorded were whether the infant had had postnatal steroids or confirmed necrotising enterocolitis, the days of invasive mechanical ventilation and parenteral nutrition prior to the MRI and the use of non-depolarising muscle relaxing agents.

Statistical analysis

Data were tested for normality with the Kolmogorov–Smirnoff test and found to be non-normally distributed. Continuous data are presented as median and interquartile range (IQR). Differences between term and premature infants were tested for significance using the Mann-Witney rank sum test. Multiple linear regression was used to adjust for confounders in differences of DCSA between term and prematurely born infants. Variables without normal distribution were logarithmically transformed. Multi-collinearity among the independent variables in the multiple regression analysis was assessed by calculation of the tolerance for the independent variables. Kendall's tau rank correlation coefficient (τ) was used to examine the relationship of DCSA with gestational age, age at MRI, birth weight, weight at measurement, days of ventilation and days of parenteral nutrition. Multiple regression analysis was used to examine the independent effect on DCSA of the parameters that were significantly related to DCSA in the bivariate analysis. Parameters with a variance inflation factor (VIF) of more than three were considered collinear.

Linear regression analysis was used to examine the relationship of DCSA to weight at MRI. The type of non-linearity was tested by visual inspection of the residuals. Statistical analysis was performed using IBM SPSS Software (IBM, Chicago IL).

RESULTS

Between 1 January 2010 and 1 June 2016, 291 infants were admitted to the neonatal unit with a gestational age of less than 28 weeks; 17 had an MRI brain scan to assess the extent of periventricular leukomalacia or ventricular dilatation. Twenty-one term infants underwent an MRI brain scan for HIE. One term infant was excluded from the study because the coronal views did not fully include the left deltoid muscle. Premature infants did not differ

from term infants in terms of gender, birth weight z-score, weight at MRI and administration of postnatal steroids. Prematurely born infants had longer durations of mechanical ventilation and parenteral nutrition and lower weight z-score at MRI than the term infants (table 1). Premature infants had lower DCSA compared to term infants (table 1) and lower DCSA compared to term infants after adjusting for weight at MRI (p=0.021, 95% Confidence Intervals: 9.628 – 111.843, Odds ratio: 0.343). DCSA was significantly related to gestational age (τ=0.545, p=0.001), birth weight z-score (τ=0.547, p=0.001), age at MRI (τ=-0.590, p<0.001), weight z-score at MRI (τ=0.658, p<0.001), days of mechanical ventilation (τ=-0.583, p<0.001), and days of parenteral nutrition (τ=-0.617, p<0.001). Following multiple regression analysis with DCSA as the outcome variable, corrected GA was excluded from the model due to collinearity with GA (VIF: 3.29) and days of parenteral nutrition were excluded from the model due to collinearity with days of mechanical ventilation (VIF: 4.32). DCSA remained significantly related to GA (adjusted p=0.003) and days of mechanical ventilation (adjusted p=0.008).

The linear regression analysis of DCSA against weight z-score at MRI is presented in figure 2. The quadratic model was found to accommodate the best non-linear fit (r^2 quadratic = 0.576).

DISCUSSION

We have demonstrated that DCSA is smaller in prematurely-born infants studied at term compared to term-born infants and that the DCSA is related to gestation, weight, duration of mechanical ventilation and duration of parenteral nutrition. Our results are in agreement with previous studies that have described that respiratory muscle strength in prematurely-born infants increases with increasing maturity [3]. Furthermore, the deleterious effect of prolonged mechanical ventilation on skeletal muscle function has been reported in adult

intensive care studies [6, 13]. In this paper we further highlight that prematurity, prolonged mechanical ventilation and parenteral nutrition (PN) are associated with reduced skeletal muscle mass acquisition. The importance of our study is that it is the first study to highlight that extremely premature infants exhibit postnatal skeletal muscle growth impairment which is related to prolonged mechanical ventilation. The duration of PN might directly represent a nutritional deficit or it might indirectly describe the cumulative severity of the intensive care stay as sicker infants will fail to advance on enteral nutrition and will require longer courses of PN.

Muscle atrophy and prolonged mechanical ventilation have an adverse synergistic relationship. Prolonged mechanical ventilation is associated with a release of pro-inflammatory cytokines [11] and the use of non-depolarizing muscle relaxants [2]. Inversely, sepsis [12] and disuse atrophy [18] directly impact on respiratory muscle function and lead to inability to wean off respiratory support. A plausible pathophysiological mechanism that explains our findings is that prolonged intensive care leads to a generalised skeletal myopathy with atrophy and necrosis of the muscle fibres and loss of myelinated nerve fibres [7, 8].

One implication of our study is that weight accretion alone might not be an adequate nutritional target in neonatal intensive care and that other anthropometric parameters should be taken into account in evaluating postnatal growth. These could include body composition analysis either by dual-energy X-ray absorptiometry, whole body MRI or bioelectrical impedance analysis. Those methods, however, have their own disadvantages such as high cost, non-availability and technical difficulties of performing serial measurements. The DCSA was indeed significantly related to weight at MRI however, given that they are both anthropometric indices, one might expect a stronger correlation. This relatively weak correlation would support the conclusion that body weight might not be the most appropriate

variable to reflect the nutritional status of these infants. Possibly, indices that incorporate information on height such as the ponderal index or the body mass index might be more appropriate.

The strengths of our study include that the radiologist who performed the DCSA measurements was blinded to the demographic and clinical details and hence was not biased in estimating the DCSA. We should acknowledge as a limitation the retrospective nature of our study and that we evaluated a selected subpopulation of premature infants that had significant intracranial pathology detected on cranial ultrasound. As such, these infants might have had a relatively more severe intensive care course. It is plausible that equally premature infants without intracranial pathology might have exhibited less prominent muscle atrophy. Our positive results emphasize the interest to study a “well' preterm population to demonstrate the independent impact of prolonged mechanical ventilation on these infants. We should also note as a limitation that the radiologist that evaluated the MRIs had access to the full images including the brain appearances. We should also note as a limitation that the radiologist that evaluated the MRIs had access to the full images including the brain appearances. The appearances of PVL or ventricular dilatation, therefore, might have had an impact on the blinding process. We thus suggest that future studies could eliminate this bias by excluding the brain from the reviewed images.

In conclusion, we have demonstrated that extremely premature infants do not accumulate/accrete muscle mass at a rate similar to their term counterparts and that prolonged ventilation in these infants is related to reduced skeletal muscle mass acquisition.

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Compliance with ethical standards

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Compliance and ethical standards: The Research and Development department confirmed that the data collection was consistent with a service evaluation/audit, and as such did not require research ethics approval. The study was registered with the Clinical Governance Department of King’s College Hospital NHS Foundation Trust.

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Informed consent: Not required.

Contributors’ statement:

T.D. conceived the study, participated in the analysis of the data, and drafted the first version of the article.

O.K. collected the data and participated in the analysis of the data.

M.K. independently reviewed the MRI scans and critically reviewed the manuscript.

A.H. contributed to study design, writing of the manuscript and interpretation of the results.

A.G. supervised the project, contributed to the study design and interpretation of the results, and critically revised the manuscript.

All authors were involved in the preparation of the manuscript and approved the final manuscript as submitted.

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Table 1: Demographics, clinical parameters and DCSA in prematurely born and term infants

Data are presented as median (IQR) or *N* (%)

	Premature	Term	
	N=17	*N*=20	p-value
Male gender	11 (65)	9 (45)	0.325*
Gestation age (weeks)	25 (24-27)	40 (38 – 41)	<0.001
CGA (weeks)	42 (40 – 48)	41 (40 – 41)	0.005
Age (days)	113 (98 – 172)	6 (4 – 8)	<0.001
Birth weight (kg)	0.76 (0.64 – 0.93)	3.56 (3.15 – 3.87)	<0.001
Birth weight z-score	-0.47 (-1.15-0.23)	0.15 (-0.81 – 0.95)	0.065
Weight at MRI (kg)	2.98 (2.59 – 4.25)	3.65 (3.20 – 4.16)	0.185
Weight at MRI z-score	-1.61 (-3.01 - -1.08)	0.14 (-1.05 – 0.79)	<0.001
Days of invasive MV	39 (14 – 62)	4 (2 – 5)	<0.001
Days of PN	34 (19 – 52)	2 (1 – 4)	<0.001
Muscle relaxing agents	3 (18)	4 (20)	0.587
Postnatal steroids	5 (27)	2 (10)	0.212*
NEC	11 (65)	0 (0)	<0.001*
DCSA (mm^2)	189 (176 – 223)	302 (236 – 389)	<0.001

Mann-Whitney U test

*Chi square

IQR: interquartile range, CGA: corrected gestation age, MRI: Magnetic resonance imaging, MV: invasive mechanical ventilation, PN: parenteral nutrition, NEC: necrotising enterocolitis, DCSA: deltoid cross sectional area.

FIGURE LEGENDS

Figure 1: Method of free hand tracing of the perimeter of the DCSA

Figure 2: Regression analysis of DCSA with weight z-score. The regression line and 95% confidence intervals are presented.

▲ male infants

O female infants